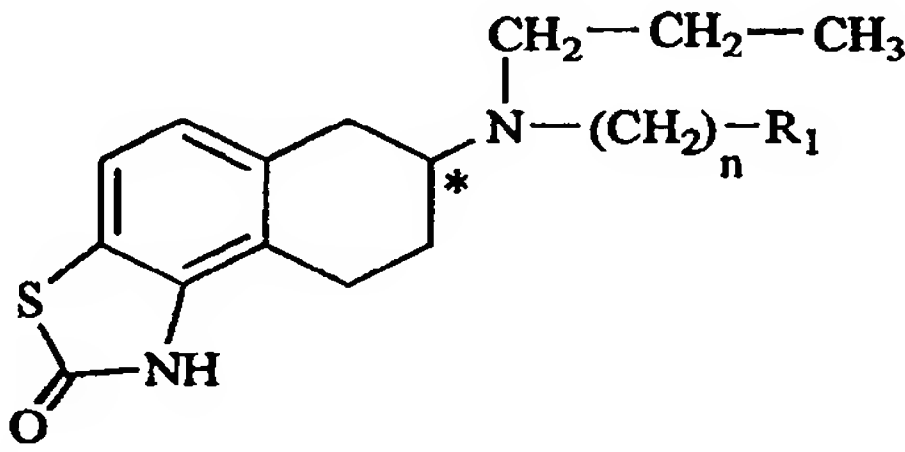




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(21) International Application Number: PCT/EP98/03560 (22) International Filing Date: 12 June 1998 (12.06.98) (30) Priority Data: MI97A001398 13 June 1997 (13.06.97) IT (71) Applicant (for all designated States except US): ZAMBON GROUP S.P.A. [IT/IT]; Via della Chimica, 9, I-36100 Vicenza (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): POCCHIARI, Felice [IT/IT]; Via A. Villa, 4, I-20091 Bresso (IT). MASOTTO, Claudio [IT/IT]; Via Martinengo, 26, I-20139 Milano (IT). CAVALLERI, Paolo [IT/IT]; Via Piave, 73, I-21047 Saronno (IT). MONTANARI, Stefania [IT/IT]; Via Martinengo, 1, I-20139 Milano (IT). SANTANGELO, Francesco [IT/IT]; Via Passo di Fargorida, 5, I-20148 Milano (IT). (74) Agent: LONGONI, Alessandra; Zambon Group S.p.A., Corporate Patents & Trademarks Dept., Via Lillo del Duca, 10, I-20091 Bresso (IT).		(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NAPHTHOTHIAZOLONE DERIVATIVES ACTIVE ON THE D ₃ DOPAMINERGIC RECEPTOR <div style="text-align: center;">  <div style="position: absolute; left: 675px; top: 585px;">(I)</div> </div> (57) Abstract <p>Naphthothiazolone derivatives of formula (I) wherein n=2 and 6; R₁ is CH₃ or an optionally substituted phenylethylenamino group, and the salts thereof are active on the D₃ receptor.</p>		

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Naphthothiazolone derivatives active on the D₃ dopaminergic receptor

The present invention relates to 4,5,6,7-tetrahydro-naphthothiazolone derivatives selectively active on the D₃ dopaminergic receptor.

The D₃ dopaminergic receptor was cloned for the first time by Sokoloff et al. (Nature, 347, 146, 1990), and is abundant in the cerebral areas connected to the emotional and cognitive functions.

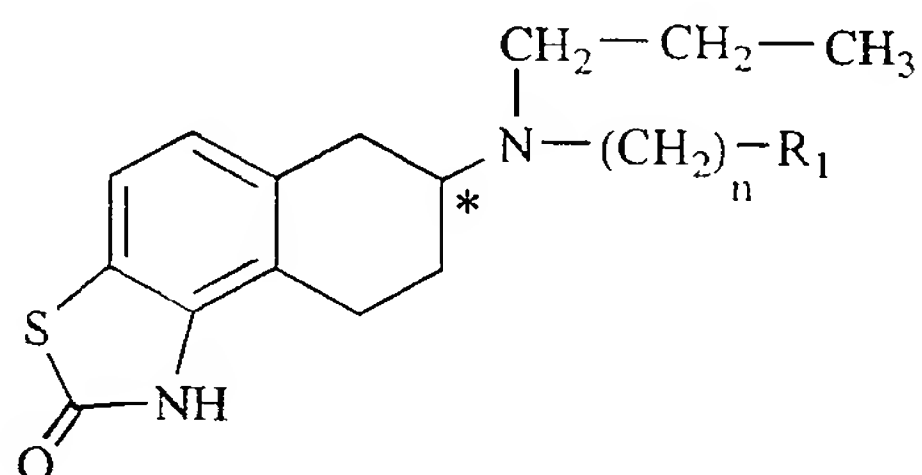
The patent application WO 96/23760 (in the name of Pharmacia & Upjohn) describes 2-aminoindanes with selective activity for the D₃ receptor.

The D₃-antagonists are said to have a potential use as antipsychotics, e.g. in the therapy of schizophrenia, schizo-emotional diseases, psychotic depression, manias. The pathologies which may be treated with the D₃-receptor agonists include dyskinesia, such as Parkinson's disease, neuroleptic parkinsonism and late dyskinesia, and also depression, anxiety, memory failure, sexual disorders, drug addiction (e.g. from cocaine).

The patent application EP 0 186 087 (in the name of Karl Thomae GmbH) discloses tetrahydrobenzothiazoles N-substituted on both the rings useful as D₂ and D₃ receptor agonists, and thus useful in the treatment of schizophrenia and Parkinson's disease. One of these compounds, 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole, is further claimed in the patent application WO 96/18395 (in the name of Upjohn/Boehringer Ingelheim) as endowed with neuroprotective effect.

We have now found a new class of compounds endowed with selective activity on the D₃ dopaminergic receptors as antagonists, agonists or partial agonists.

Therefore the present invention relates to compounds of formula I

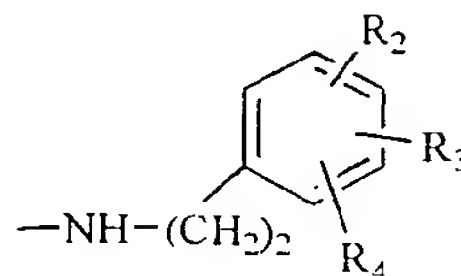


(I)

- 2 -

wherein n is an integer comprised between 2 and 6;

R₁ is a methyl group or a group



5

wherein R₂, R₃ and R₄ are independently hydrogen, hydroxy, methoxy, methylsulfonyl, or one of R₂, R₃ and R₄ together with another one of the three substituents forms a -O-CH₂-O- bridge;

the asterisk marks an asymmetric carbon atom;

10 and the pharmaceutically acceptable salts thereof.

The compounds of formula I have at least an asymmetric centre, marked by an asterisk, and may therefore be in form of stereoisomers.

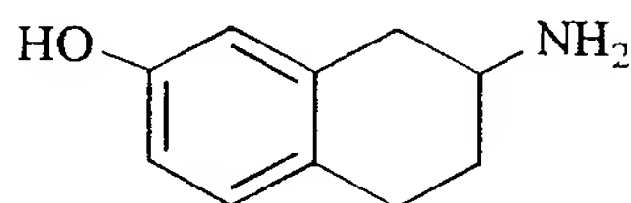
Object of the present inventions are the compounds of formula I in form of stereoisomeric mixture and also as single stereoisomers.

15 The compounds of formula I are active on the D₃ dopaminergic receptors also by oral route. They are therapeutically useful in the treatment of psychotic diseases, such as schizophrenia, dyskinesia, such as Parkinson's disease, of depression, anxiety, memory diseases, sexual disorders and drug addiction.

Preferred compounds of formula I are the ones wherein the carbon atom marked by
20 an asterisk has the S configuration.

Pharmaceutically acceptable salts of the compounds of formula I are salts with organic and inorganic acids such as, e.g., hydrochloric, hydrobromic, hydroiodic, nitric, sulphuric, phosphoric, acetic, benzoic, maleic, fumaric, succinic, citric, aspartic, methansulfonic and 3,7-di-t.butyl-naphthalen-1,5-disulfonic (dibudinic acid).

25 The preparation of the compounds of formula I is effected according to methods known by the skilled in the art. For example, a compound of formula II



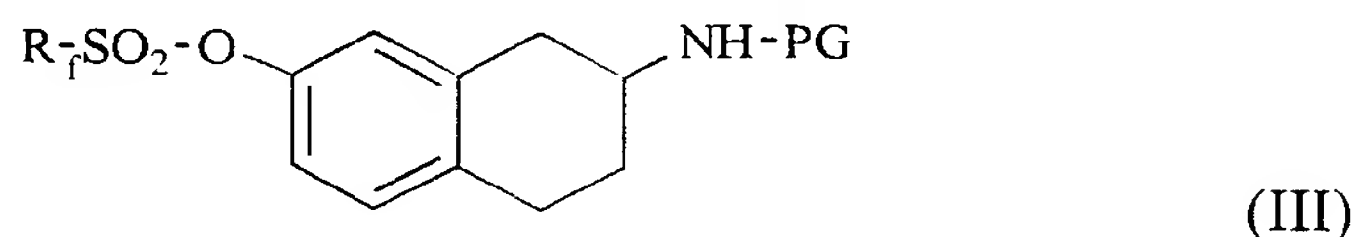
(II)

30 or a salt thereof is duly protected on the amino group, for example with di-tert-butylcar-

- 3 -

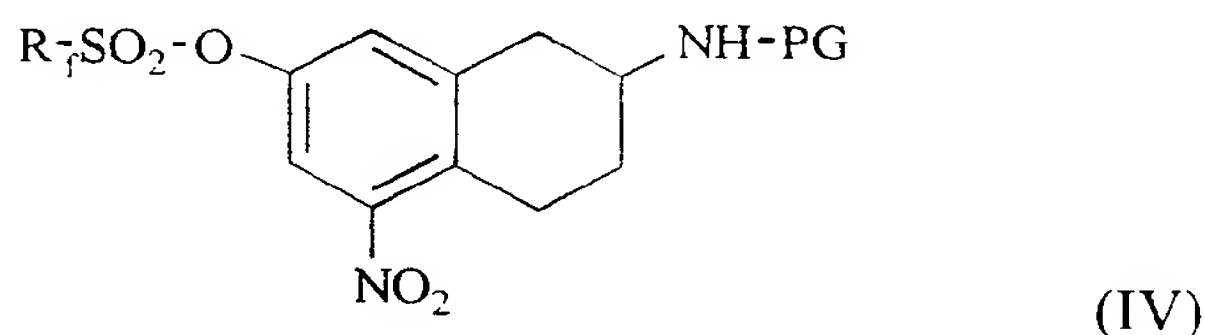
bonate, phthalic anhydride or trifluoroacetic anhydride; the hydroxy group is then turned into a polyfluoroalkylsulfonyloxy group (R_fSO_2O-) such as, for example, trifluoromethylsulfonyloxy, thereby yielding a compound of formula III

5



wherein R_f is a lower polyfluoroalkyl group and PG a protecting group, which is nitrated for example with nitric acid or other nitrating agents such as ammonium nitrate/trifluoroacetic anhydride or nitronium tetrafluoroborate, to give a compound of formula IV

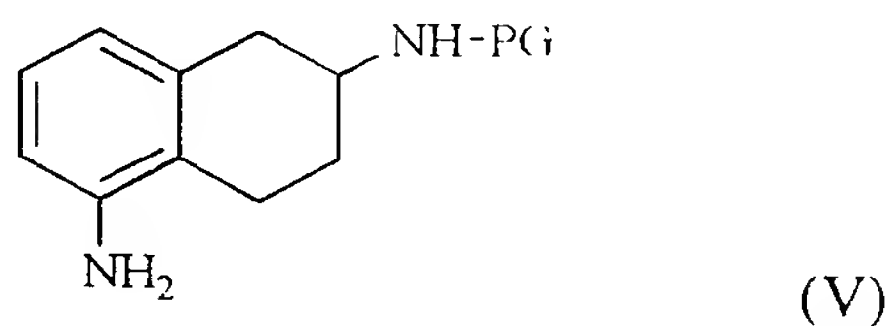
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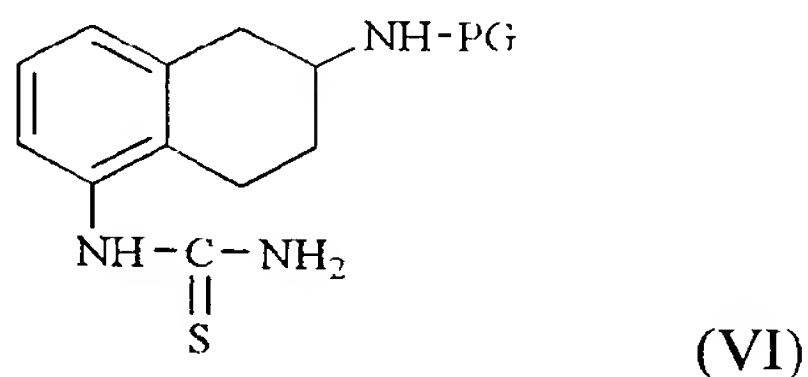
wherein R_f and PG are as defined above. The nitro group of the compound of formula IV is reduced to amino by hydrogenation in the presence of a catalyst made of a metal such as palladium, platinum, nickel, rhodium and ruthenium; in the meantime the polyfluoroalkylsulfonyloxy group is reduced, thus obtaining a compound of formula V

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wherein PG is as defined above, which is reacted with a thiocyanate such as, for example, ammonium or alkali metal thiocyanate, in acidic environment to give a compound of formula VI

25



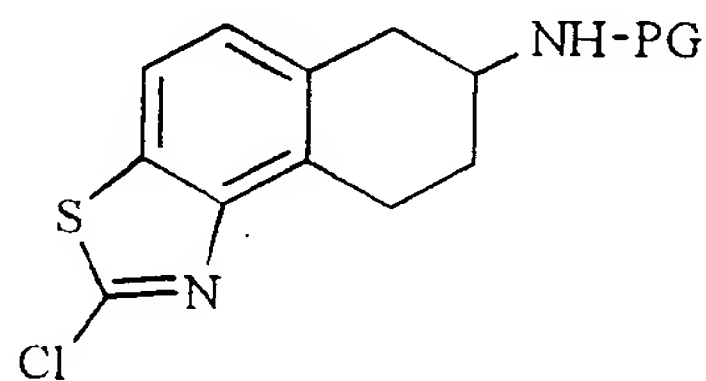
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wherein PG is as defined above. This compound is cyclized to an aminothiazole de-

- 4 -

rivative by heating in the presence of thionyl chloride or bromine in chloroform, and then turned in the equivalent diazonium salt applying known techniques. The diazonium salt is turned in the compound of formula VII

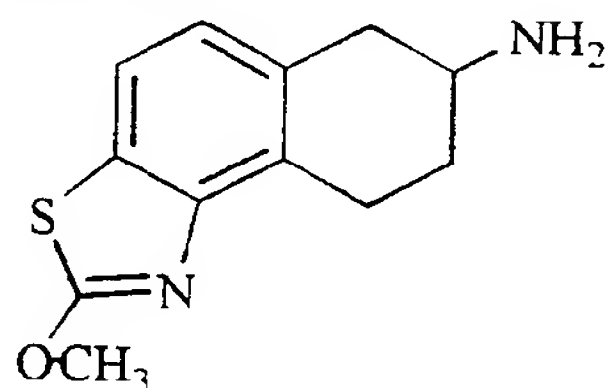
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(VII)

10 wherein PG is as defined above, by treatment with copper(I)chloride. Alternatively, the compound of formula VII may be directly obtained from the aminothiazole compound by treatment with copper(II)chloride and t-butyl nitrite. The compound of formula VII is reacted with sodium methylate and then the amino group is deprotected to give a compound of formula VIII

15

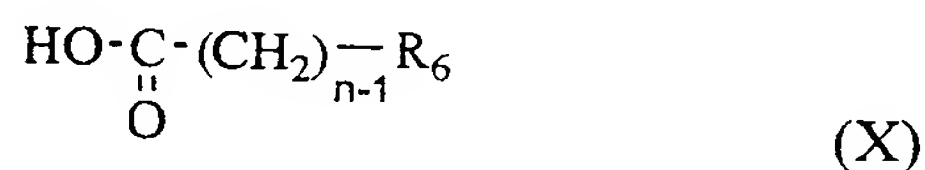


(VIII)

20 which is reacted with propionic aldehyde in the presence of sodium cyanoborohydride or under other conditions for reductive amination.

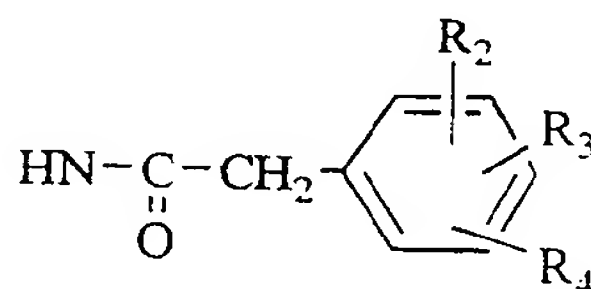
The compound of formula IX is reacted under dehydrating conditions with an acid of formula X

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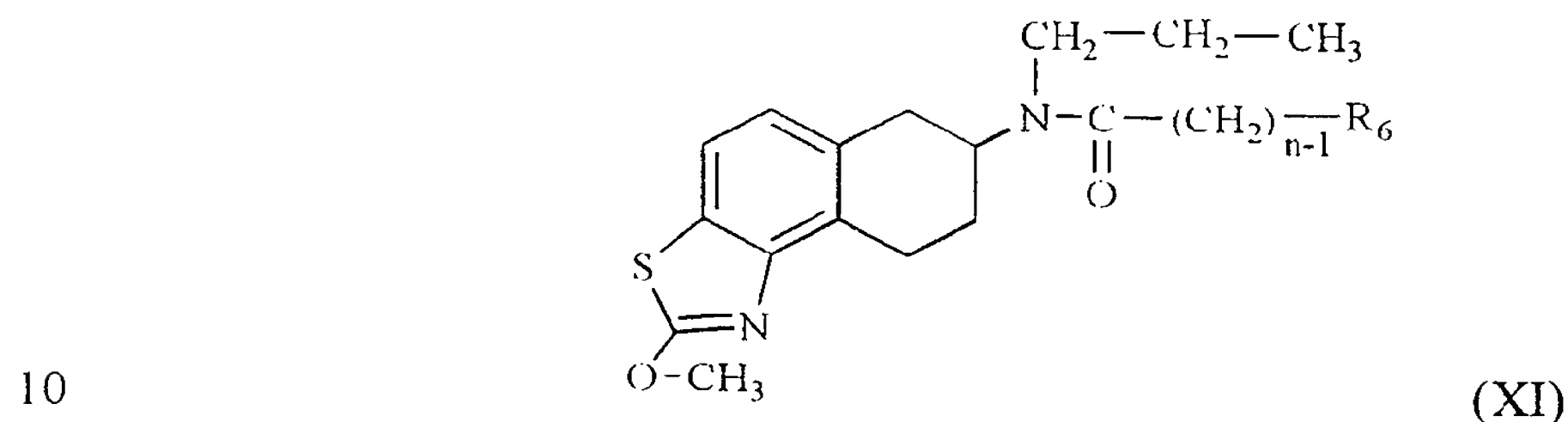
wherein n is as defined above and R₆ is hydrogen or a group

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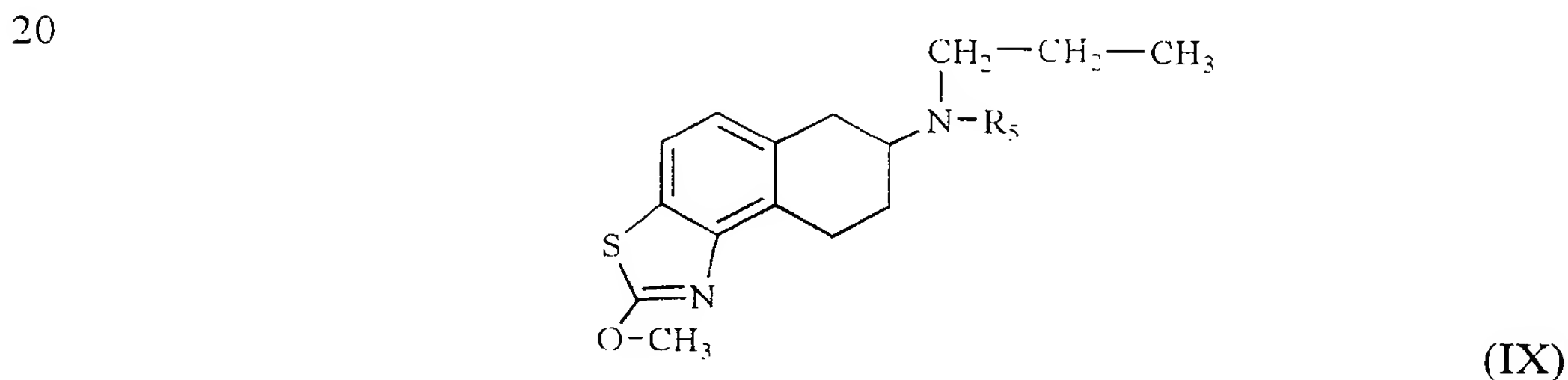
wherein R_2 , R_3 and R_4 are as defined above, or with a reactive derivative thereof such as an acyl halide or a mixed anhydride which may also be prepared *in situ*, in an inert solvent in the presence of a base such as an alkali carbonate or bicarbonate or a tertiary amine, to give an intermediate of formula XI



wherein n and R_6 are as defined above, which is treated with hydrochloric acid in hot tetrahydrofuran and subsequently reduced on all the present amido groups by a reducing agent such borane or borane complexes, for example, with methylsulfide or lithium aluminium hydride, to give the compounds of formula I.

A specific alternative relates to the compounds of formula I wherein n is 2 and R_1 is methyl which may be prepared by reacting the compound of formula VIII above with a double amount of propionic aldehyde under the just mentioned conditions.

A compound of formula IX is thus obtained



25

wherein R_5 is hydrogen or a propyl group. The treatment of the compound of formula IX wherein R_5 is propyl with hydrochloric acid in dioxane and methanol allows the obtainment of the compounds of formula I wherein R_1 is methyl and $n=2$.

The compounds of formula I in optically active form are obtained by optical separation or through stereospecific or stereoselective synthesis.

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The preparation of the salts of the compounds of formula I is carried out according to conventional methods.

5 The compounds of formula I are active on the D₃ dopaminergic receptors. The interaction test with other receptorial systems showed that the compounds of formula I do not notably interact and thus they are endowed with high specificity (Example 12).

It is apparent that these selectivity and specificity features make the compounds of formula I particularly suitable for the treatment of central diseases and in the antipsychotic therapy, in that of the dyskinesia, in the treatment of depression, anxiety,
10 memory problems, sexual disorders and drug addiction.

Moreover these compounds may be used as selective markers for the D₃ receptors optionally in form of radioligands.

As a consequence in the therapeutical practice the compounds of formula I may be administered both parenterally and enterally. The therapeutical doses usually range
15 between 0.1 mg and 400 mg a day by oral route for single administration.

Another object of the present invention are the pharmaceutical compositions containing a therapeutically effective amount of the compounds of formula I or the pharmaceutically acceptable salts thereof in admixture with a suitable carrier.

The pharmaceutical compositions of the invention may be liquid, suitable to the enteral or parenteral administration, and, preferably, solid such as tablets, capsules,
20 granulates, suitable to the oral administration.

The preparation of the pharmaceutical compositions of the invention may be carried out according to common techniques.

A further object of the invention relates to diagnostic kit containing one of the compounds of formula I optionally in form of radioligand.
25

For better illustrating the present invention the following examples are now provided. The chromatographic purifications were effected on silica gel columns (230-400 mesh). Unless otherwise specified, the mass spectra were effected under the following conditions: chemical ionisation, isobutane, positive ions.

30

Example 1

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Synthesis of (S)-7-trifluoroacetylamino-5,6,7,8-tetrahydro-2-naphthyl trifluoromethansulfonate

A suspension of 7-hydroxy-1,2,3,4-tetrahydro-2-naphthylamine hydrobromide (12.2 g; 50 mmoles) (prepared as described in the patent application FR 2653765 in the name of Midy) and triethylamine (25 ml; 175 mmoles) in CH_2Cl_2 (400 ml) and acetonitrile (20 ml), under stirring at room temperature, was dropwise added with a solution of trifluoroacetic anhydride (8.3 ml; 57.5 mmoles) in CH_2Cl_2 (100 ml). After 2 hours water was added (200 ml). The organic phase was washed first with a 1N solution of HCl (200 ml) then with water (200 ml), anhydri-fied over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude was dissolved in acetonitrile (300 ml). The resulting solution was added with K_2CO_3 (12.5 g; 90.7 mmoles) and, dropwise, with a solution of N-phenyltrifluoromethansulfonimide (17 g; 47.6 mmoles) in acetonitrile (100 ml) at room temperature. The mixture was stirred at room temperature for 18 hours, then the solvent was evaporated under reduced pressure. The residue was added with ethyl ether (600 ml) and water (300 ml). The phases were separated and the organic one washed first with a 1N solution of HCl (300 ml) then with water (300 ml), anhydri-fied over Na_2SO_4 , and the solvent evaporated under reduced pressure. The crude was purified by silica gel chromatography (eluent petrolatum:ethyl acetate = 8:2).

There were obtained 16.1 g of (S)-7-trifluoroacetylamino-5,6,7,8-tetrahydro-2-naphthyl trifluoromethansulfonate.

^1H -NMR (200 MHz, CDCl_3): δ (ppm) 1.75-1.97 (m, 1H); 2.07-2.22 (m, 1H); 2.76 (dd, 1H); 2.87-2.98 (m, 2H); 3.20 (dd, 1H); 4.20-4.40 (m, 1H); 6.33 (bd, 1H); 6.97 (d, 1H); 7.05 (dd, 1H); 7.18 (d, 1H).

Mass: 392 (M + H) $^+$.

Example 2

Synthesis of (S)-4-nitro-7-trifluoroacetylamino-5,6,7,8-tetrahydro-2-naphthyl trifluoromethansulfonate

A solution of (S)-7-trifluoroacetylamino-5,6,7,8-tetrahydro-2-naphthyl trifluorometh-

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ansulfonate (15.8 g, 40.4 mmol), prepared as described in example 1, in trifluoroacetic acid (150 ml), under stirring at 0°C, was dropwise added with 100% HNO₃ (2.1 ml; 52.5 mmol). At the end of the addition the mixture was left to rise to room temperature and after 50 minutes poured into water and ice (1200 ml). The formed precipitate was filtered and dissolved in ethyl ether (600 ml). The organic phase was washed with water (2x300 ml), anhydried over anhydrous Na₂SO₄ and the solvent evaporated under reduced pressure. The resulting crude was purified by silica gel chromatography (eluent petrolatum:ethyl acetate = 8:2).

There were obtained 9.8 g of (S)-4-nitro-7-trifluoroacetylamino-5,6,7,8-tetrahydro-2-naphthyl trifluoromethanesulfonate.

¹H-NMR (200 MHz, CDCl₃): (ppm) 1.74-1.97(m,1H); 2.15-2.31(m,1H); 2.89(dd, 1H); 3.12-3.24(m,2H); 3.38(dd,1H); 4.21-4.41(m,1H); 6.38(bd,1H); 7.28(d,1H); 7.72 (d,1H).
Mass: 437 (M + H)⁺.

Example 3

Synthesis of (S)-N-(5-amino-1,2,3,4-tetrahydro-2-naphthyl)trifluoroacetamide

A mixture of (S)-4-nitro-7-trifluoroacetylamino-5,6,7,8-tetrahydro-2-naphthyl trifluoromethanesulfonate (9.8 g; 22.5 mmol), prepared as described in example 2, and triethylamine (8.2 ml; 56.2 mmol) in methanol (500 ml) was kept under hydrogen pressure (50 psi=3.4 atm) in the presence of 10% Pd/C (5 g) for 1.5 hour at room temperature. After filtering off the catalyst the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (300 ml) and the solution washed with water (3x200 ml), anhydried over anhydrous Na₂SO₄ and the solvent evaporated under reduced pressure. The crude was purified by silica gel chromatography (eluent methylene chloride:methanol = 98:2).

There were obtained 4.4 g of (S)-N-(5-amino-1,2,3,4-tetrahydro-2-naphthyl)-trifluoroacetamide.

¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.83-2.24(m,2H); 2.58(m,2H); 2.71(dd,1H); 3.12(dd,1H); 3.60(bs,2H); 4.22-4.41(m,1H); 6.26(bd,1H); 6.55(m,2H); 6.99 (m, 1H).

Mass (electronic impact): 258 (M + H)⁺.

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The product was subsequently turned into the corresponding hydrochloride by dissolution into ethyl acetate saturated with HCl followed by evaporation of the solvent under reduced pressure.

5

Example 4

Synthesis of (S)-6-trifluoroacetylamino-5,6,7,8-tetrahydro-1-naphthylthiourea

A suspension of (S)-1,2,3,4-tetrahydro-1,5-naphthalendiamine-2-trifluoroacetamide hydrochloride (4.4 g; 14.9 mmol), prepared as described in example 3, in chlorobenzene (45 ml), under stirring at 50°C, was added with 12N HCl (0.13 ml) and ammonium thiocyanate (2.27 g; 29.9 mmol). The mixture was heated to 115°C for 3 hours. After evaporating the solvent under reduced pressure the resulting residue was added with ethyl acetate (200 ml) and water (100 ml). The organic phase was washed with water (100 ml), anhydried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The resulting crude was purified by silica gel chromatography (eluent methylene chloride:methanol = 95:5).

15

There were obtained 3 g of (S)-6-trifluoroacetylamino-5,6,7,8-tetrahydro-1-naphthylthiourea.

¹H-NMR (200 MHz, DMSO-d₆): δ (ppm) 1.59-2.08 (m, 2H); 2.61-3.08 (m, 4H); 3.91-4.13 (m, 1H); 6.98-7.19 (m, 3H); 9.16 (bs, 1H); 9.49 (bd, 1H).

20

Mass (thermospray): 318 (M + H)⁺.

Example 5

Synthesis of (S)-2-chloro-6-trifluoroacetylamino-4,5,6,7-tetrahydronaphtho(1,2-d)-thiazole

A solution of (S)-6-trifluoroacetylamino-5,6,7,8-tetrahydro-1-naphthylthiourea (2.6 g; 8.2 mmol), prepared as described in example 4, in thionyl chloride (4 ml) was heated to 60°C for 1.5 hour. After cooling to 0°C water was added (50 ml) and the mixture heated again to 80°C for 2 hours, then brought to room temperature, alkalinised with 30% ammonia and extracted with ethyl acetate. The organic phase was washed with water, anhydried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The residue was dissolved in ethyl acetate. After adding ethyl

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- 10 -

acetate saturated with HCl a precipitate was obtained, filtered on a porous sect and washed with petrolatum on the filter. The resulting solid, dried under vacuum at 50°C overnight, was portionwise added to a suspension of copper(II)chloride (1 g; 7.4
5 mmoles) and t-butylnitrite (1.1 ml; 9.2 mmoles) in dry acetonitrile (50 ml), under stirring at 60°C. After 25 minutes the reaction mixture was brought to room temperature and poured into 20% HCl. After extraction with ethyl ether the organic phase was washed first with 2N HCl then with water, anhydrified over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The resulting crude was purified by
10 silica gel chromatography (eluent petrolatum:ethyl acetate = 8:2).
There were obtained 1.4 g of (S)-2-chloro-6-trifluoroacetyl-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole.
¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.84-2.07(m, 1H); 2.14-2.31(m, 1H); 2.83(dd, 1H); 3.13-3.49(m, 3H); 4.20-4.39 (m, 1H); 6.32 (bd, 1H); 7.12 (d, 1H); 7.55 (d, 1H).
15 Mass (thermospray): 335 (M + H)⁺.

Example 6

Synthesis of (S)-2-methoxy-6-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole

Sodium (0.22 g; 9.6 mmoles) was portionwise added to dry CH₃OH (30 ml), under stirring at room temperature. When the dissolution was completed a portion of (S)-2-chloro-6-trifluoroacetyl-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole (1.4 g; 4.2
20 mmoles), prepared as described in example 5, was added and the mixture refluxed for 5 hours. After cooling to room temperature water (2 ml) and a 32% solution of NaOH (0,5 ml) were added and the mixture was refluxed again for 2 hours. After evaporation of the solvent under reduced pressure the residue was added with methylene chloride and water. The phases were separated and the organic one was washed
25 with a saturated solution of NaCl, anhydrified over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure.

There was obtained 0.95 g of (S)-2-methoxy-6-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole.
30 ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.43 (bs, 2H); 1.51-1.74 (m, 1H); 2-2.17 (m,

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1H); 2.6 (m, 1H); 2.89-3.4 (m, 4H); 4.16 (s, 3H); 6.93 (d, 1H); 7.38 (d, 1H).

Mass (thermospray): 235 (M + H)⁺.

Example 7

5 Synthesis of (S)-2-methoxy-6-dipropylamino-4,5,6,7-tetrahydronaphtho(1,2-d)-thiazole

A solution of (S)-2-methoxy-6-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole (0.1 g; 0.42 mmol), prepared as described in example 6, in CH₃OH (5 ml), under stirring at room temperature on 3 Å molecular sieves, was added with sodium acetate (56 mg; 0.68 mmol), sodium cyanoborohydride (54 mg; 0.85 mmol) and propionic aldehyde (0.09 ml; 1.26 mmol). After 18 hours the reaction mixture was poured into water. After extraction with ethyl acetate the organic phase was washed with a saturated solution of NaCl, anhydried over Na₂SO₄ and concentrated to dryness under reduced pressure. The resulting crude was purified by silica gel chromatography (eluent methylene chloride:methanol: 30% ammonia = 90:10:0.5).

There were obtained 108 mg of (S)-2-methoxy-6-dipropylamino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole.

¹H-NMR (200 MHz, CDCl₃): δ (ppm) 0.89(t,6H); 1.37-1.75(m,5H); 2.03-2.18(m,1H); 2.49(m,4H); 2.71-3.09(m,4H); 3.40(m,1H); 4.16(s,3H); 6.95(d,1H); 7.37(d,1H).

Mass (thermospray): 319 (M + H)⁺.

Example 8

Synthesis of (S)-6-dipropylamino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazol-2(3H)-one hydrochloride (Compound 1)

25 A solution of (S)-2-methoxy-6-dipropylamino-4,5,6,7-tetrahydronaphtho(1,2-d)-thiazole (0.1 g; 0.31 mmol), prepared as described in example 7, in methanol (1 ml) and dioxane (3 ml) was added with 3 drops of 37% HCl. The mixture was stirred at room temperature for 6 hours, then the solvents were evaporated under reduced pressure.

There were obtained 107 mg of (S)-6-dipropylamino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazol-2(3H)-one hydrochloride.

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¹H-NMR (200 MHz, D₂O): δ (ppm) 0.84 (t, 6H); 1.50-2.23 (m, 6H); 2.47-3.14 (m, 8H); 3.49-3.66 (m, 1H); 6.81 (d 1H); 7.10 (d, 1H).

Mass (thermospray): 305 (M + H)⁺.

5

Example 9

Synthesis of (S)-2-methoxy-6-propylamino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole

A solution of (S)-2-methoxy-6-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole (0.35 g; 1.49 mmol), prepared as described in example 6, in methanol (15 ml), under stirring at room temperature on 3 Å molecular sieves, was added with sodium acetate (196 mg; 2.4 mmol), sodium cyanoborohydride (188 mg; 3 mmol) and propionic aldehyde (0.107 ml; 1.49 mmol). After 25 hours the mixture was evaporated to dryness under reduced pressure and the resulting residue was added with ethyl acetate and water. The phases were separated and the organic one was washed with a saturated solution of NaCl, anhydried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The resulting crude was purified by silica gel chromatography (eluent methylene chloride:methanol:30% ammonia= 90:10:0.5).

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There were obtained 270 mg of (S)-2-methoxy-6-propylamino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole.

¹H-NMR (200 MHz, CDCl₃): δ (ppm) 0.93 (t, 3H); 1.43-2.21 (m, 5H); 2.57-3.14 (m, 6H); 3.30 (m, 1H); 4.16 (s, 3H); 6.95 (d, 1H); 7.37 (d, 1H).

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Mass (thermospray): 277 (M + H)⁺.

Example 10

Synthesis of (S)-6-N-propyl-N-6-[(4-methylsulfonylphenyl)acetyl-amino]-1-keto-hexyl-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazol-2(3H)-one

A suspension of 6-(4-methylsulfonylphenyl)acetamidohexanoic acid (320 mg; 0.95 mmol) in methylene chloride (5 ml) was added under stirring at room temperature with thionyl chloride (0.082 ml; 1.13 mmol). After 1.5 hour the solvent and the exceeding thionyl chloride were evaporated under reduced pressure. The resulting oil was dissolved in methylene chloride (5 ml) and the obtained solution was dropwise added, under stirring at room temperature, to a solution of (S)-2-methoxy-6-propyl-

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amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazole (240 mg; 0.87 mmoles), prepared as described in example 9, and triethylamine (0.38 ml; 2.6 mmoles) in methylene chloride (20 ml). After 1 hour the reaction mixture was poured into water and methylene chloride. The organic phase was washed first with a 5% solution of KHCO_3 then with water, anhydriified over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure, the residue was dissolved in THF (15 ml) and the solution was added with 3 drops of 37% HCl. The reaction mixture was heated to 60°C for 6 hours, then evaporated to dryness under reduced pressure and the resulting residue was added with methylene chloride and water. The phases were separated and the organic one was washed with water, anhydriified over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The obtained crude was purified by silica gel chromatography (eluent methylene chloride:methanol = 9:1).

There were obtained 450 mg of (S)-6-N-propyl-N-6-[(4-methylsulfonylphenyl)acetyl-amino]-1-keto-hexyl-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazol-2(3H)-one.

$^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 0.90 and 0.93 (2t, 3H); 1.22-2.18 (m, 10H); 2.29-2.41 (m, 2H); 2.72-3.36 (m, 8H); 3.02 and 3.04 (2s, 3H); 3.60 (s, 2H); 3.89-4.11 and 4.47-4.69 (2m, 1H); 6.25 and 6.39 (2bt, 1H); 6.79-6.93 (2d, 1H); 7.09-7.23 (2d, 1H); 7.43-7.90 (m, 4H); 9.83 and 9.90 (2bs, 1H).

Mass (thermospray): 572 ($\text{M} + \text{H}$) $^+$.

Example 11

Synthesis of (S)-6-N-propyl-N-6-[2-(4-methylsulfonylphenyl)ethylamino]hexylamino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazol-2(3H)-one dihydrochloride (Compound 2)

A solution of (S)-6-N-propyl-N-6-[(4-methylsulfonylphenyl)acetyl-amino]-1-keto-hexyl-amino-4,5,6,7-tetrahydronaphtho(1,2-d)thiazol-2(3H)-one (300 mg; 0.52 mmoles), prepared as described in example 10, in dry THF (15 ml) was dropwise added with borane methylsulfide (0.4 ml; 4.2 mmoles) under stirring at room temperature. At the end of the addition the mixture was refluxed for 3 hours. After cooling to 5°C a solution of 37% HCl (0.4 ml) in methanol (4 ml) was dropwise added, the mixture was refluxed again for 3 hours. The crude obtained after

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evaporation of the solvents under reduced pressure was purified by silica gel chromatography (eluent methylene chloride:methanol:50% formic acid= 85:15:2). The resulting product was dissolved in absolute ethanol and this solution was brought to
5 neatly acid pH by adding ethyl ether saturated with HCl. After evaporation under reduced pressure there were obtained 210 mg of (S)-6-N-propyl-N-6-(2-(4-methylsulfonylphenyl)-ethyl-amino)hexyl-amino-4,5,6,7-tetrahydronaphtho-(1,2-d)-thiazol-2(3H)-one dihydrochloride.

¹H-NMR (200 MHz, D₂O): δ (ppm) 0.84 (t, 3H); 1.23-2.26 (m, 12H); 3.07 (s, 3H);
10 2.51-3.23 (m, 14H); 3.56-3.72 (m, 1H); 6.83-7.13 (m, 2H); 7.36-7.74 (m, 4H).
Mass (thermospray): 544 (M + H)⁺.

Example 12

Test for evaluating the binding to dopaminergic receptors in cell cultures

Chinese hamster ovary cells (CHO) transfected with dopaminergic receptor subtypes
15 and murine mesencephalic neuronal (NM9D) expressing the different subtypes of such receptors were used. The cell lines were grown on Petri dishes, in a mixture of DMEM and Ham's F12 medium 1:1 supplemented with 10% foetal bovine serum (FBS), penicillin, streptomycin, geneticin (500 µg/ml) and glutamin in a humidified 5% CO₂ atmosphere at 37°C. When cells reached confluence they were washed with 10 ml of
20 PBS (KCl 2.68mM, KH₂PO₄ 1.4mM, NaCl 0.13mM and Na₂HPO₄ 6.4mM) then 5 ml of lysis buffer (Tris-HCl 10mM and EDTA 5mM) were added to each Petri. Cells were scrapped and the solution centrifuged for 20 minutes at 48,000 gravity, 4°C. The pellet was suspended in a minimal amount of lysis buffer and homogenised for 15 seconds. The membrane solution was aliquotated in portions of from 1 to 1.5 ml at a
25 protein concentration of about 3 mg/ml (measured by a Bio-Rad protein assay based on the differential change of colour of a dye in response to different concentration of protein), placed in plastic tubes, rapidly frozen in liquid nitrogen and stored at -80°C.
The binding test was performed as reported by Billard et al., 1984, Life Sciences, 35, 1885-1893, Seabrook et al., 1992, FEBS, 312, 123-126 and Sunahara et al. 1991,
30 Nature, 350, 614-619. For saturation experiments [3H]-SCH23390 (Amersham;

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specific activity=70 Curie/mmol) was used as radioligand for D₁ receptors, D₅ and [3H]-spiperone (Amersham; specific activity=113 Curie/mmol) for D₂, D₃ and D₄ receptors. Saturation curves were analysed using Ligand[®] program to have K_d (dissociation constant) and B_{max} (number of receptors/mg of protein) (Munson and Rodbar, 1980, Anal. Biochem., 107, 220-239).

Displacement studies were performed on cell membrane at the following conditions:

Receptor	Radioligand	Radioligand Concentration	Non specific
D ₁	[3H]-SCH23390	0.2nM	(-)-cis-flupenthixol (1μM)
D ₅	[3H]-SCH23390	0.2nM	(-)-cis-flupenthixol (1μM)
D _{2s}	[3H]-spiperone	0.1nM	(+)-butaclamol (1μM)
D ₃	[3H]-spiperone	0.3nM	(+)-butaclamol (1μM)
D ₄	[3H]-spiperone	0.2nM	(+)-butaclamol (1μM)

The compounds of the invention were tested at increasing concentrations for evaluating their binding to the various receptors, expressed as K_i (affinity constant) obtained through the Cheng and Prusoff equation

The results are shown in Table 1.

Table 1

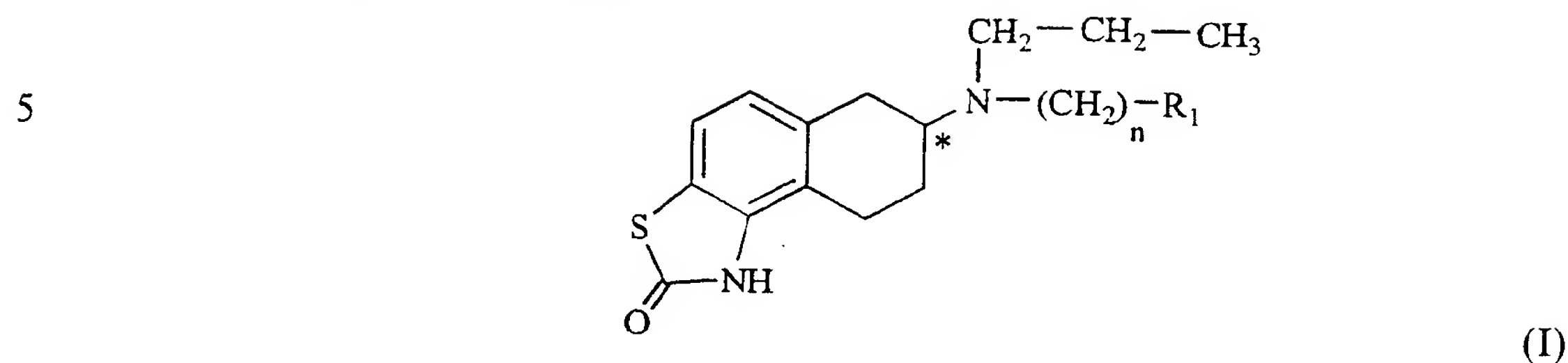
Compound	Receptor binding (K _i nM)				
	D ₁	D ₅	D _{2s}	D ₃	D ₄
1	>10 ⁴	>10 ⁴	n.d.	489	9841
2	>10 ⁴	9273	9440	92	>10 ⁴

The compounds of formula I show to selectively bind D₃ receptor having an affinity constant for the remaining tested receptors neatly higher.

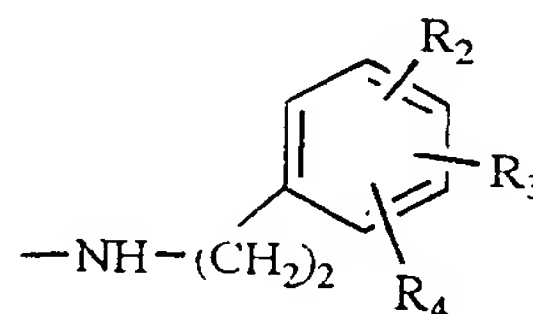
- 16 -

Claims

1) A compound of formula



wherein n is an integer between 2 and 6;

10 R₁ is a methyl group or a group

15 wherein R₂, R₃ and R₄ are independently hydrogen, hydroxy, methoxy, methylsulfonyl, or one of R₂, R₃ and R₄ together with another one of the three substituents forms a -O-CH₂-O- bridge;

the asterisk marks an asymmetric carbon atom;

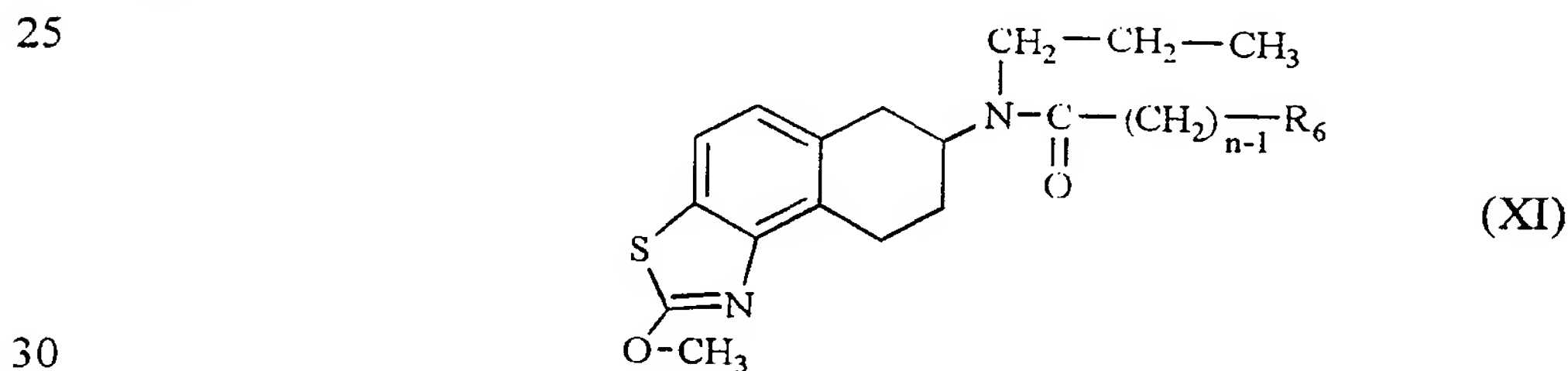
and the pharmaceutically acceptable salts thereof.

20 2) A compound according to claim 1 wherein the carbon atom marked by an asterisk has the S configuration.

3) A compound according to claim 1 in optically active form.

4) A process for preparing a compound according to claim 1 comprising the reduction and the subsequent treatment with hydrochloric acid of a compound of formula

XI



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03560

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D277/84 A61K31/425 A61K51/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 21608 A (THE UPJOHN COMPANY) 29 September 1994 see claims -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

1 October 1998

Date of mailing of the international search report

08/10/1998

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 98/03560

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